

DEVICE'S NOTEBOOK

ABOUT US

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CONSIDERATIONS

What we have to determine:

WEDNESDAY, MAY 4TH

- How effectively diffusivity works
- Scaling:
 - Model and prototype
 - Measurements
- Layers:
 - Kill switch in backing layer and bottom layer
 - Break controller
- Know how long proteins would stay in the body

FRIDAY, MAY 6TH

- Habitation:
 - Reservoir/chamber
 - Control temperature
 - Oxygen permeability
 - Specific parts of the body (heat, placement)
 - Delivery of nutrients - snapping mechanism?
 - Modelling - in different conditions, see the growth rate
- Entire Device:
 - Design
 - Materials - contaminants
 - Eg) rate controlling membranes, diffusion of peptides
- Interface:
 - Needle - size, density, material, design
 - Compatibility - initiation
 - Site of application
 - Disinfect prior to use, etc.

FRIDAY, MAY 20TH

- General
 - How to apply to body?
 - How to discard after use (i.e. when we take it out, won't the media start to leak?)
- Microneedles/Drug Reservoir
 - How to deliver drug through microneedle? (frozen, snap mechanism, isotonic?)
 - Hollow needle location → side or straight down?
 - What to test? (strain, stress, flow rate, diffusivity, etc.)
 - How to construct everything on a small scale?
 - Can we build a microneedle based on our own dimensions (i.e. can we customize the microneedle)? Or are the dimensions preset because we are ordering them in?

- Backing layer → is that included in the microneedle or do we need to attach it on?
- Actually getting microneedles
- What is in the drug reservoir? (bacteria, nutrients (LB = nutrients))
- Can we build on a microscopic scale? If so, how?
- What is the media that is in the microneedle?
- How do traditional microneedles work?
- Snapping mechanism
- Size-controlling membrane
 - How big should the pores be? (0.1 micrometer or smaller... 0.1 = size before bacteria can go through) → what else other than peptides will go into the body? Will they be harmful?
 - What material should it be made of? What else do we need to consider for the membrane (flexibility, etc.)?
 - How do we get it? (3M)?
 - Can we cut it to get it in a certain size?

WEDNESDAY, MAY 25TH

When researching materials, consider the following:

- cost
- environmentally friendly
- the “biological aspects” (e.g. gas/oxygen permeability, elasticity permeable)
- how can we get the material (local, international)
- think about how can we use the material to assemble the device (e.g. if we need silicon for the device for example, is it easily machined?)

TUESDAY, MAY 31ST

***The patch has to be **transparent** so that the indicator can be noticeable

MONDAY, JUNE 6TH

- How to make the patch **long term**
 - Look at disposable
 - Space the package would take
 - Shelf life, how long would it take for the patch contents to “expire”
- Think about the worse scenarios that we could get
 - Then we can start thinking about alternatives
 - 100 mL vs. 10 mL
 - Packets being unintentionally popped
- Actually have a plan, but it is also important to know how everything works out

DESIGNS

MONDAY, MAY 9TH

DESIGN OF MICRONEEDLES:

- Hollow cylindrical microneedle with conical tip
- Enough strength to withstand bending and axial forces
- Pressure uniform in main cavity of needle
- Velocity constant in cavity; increase in outlet
- Flow rate controlled by applied pressure and diameter of hole
- For different materials - strength and deformation compared

Design 1:

- The microneedle - from the machine shop
- Semipermeable membrane - use a filter (different grades of filter paper)
- Bacteria?
- A top layer (to the bacteria)

Design 2:

Part 1: MICRONEEDLE

- The microneedle - from machine shop
- Semipermeable membrane - use a filter (use different grades of filter paper)

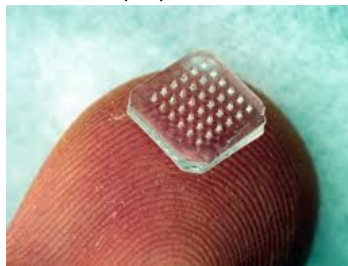
Part 2: CAPSULE WITH BACTERIA

- Capsule with bacteria - the capsule can be put in the fridge; after, it would be inserted into the microneedle and then using a snapping mechanism/force to break the capsule which starts the process and peptides go through the semipermeable membrane

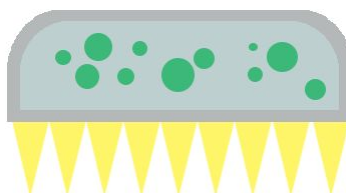
TUESDAY, MAY 17TH

Device Prototypes:

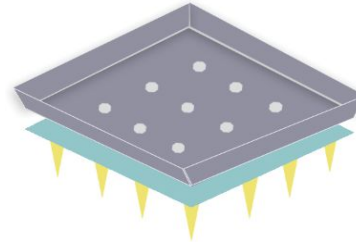
- Major idea #1: Bacteria, rich media (LB), membrane all in top of drug reservoir



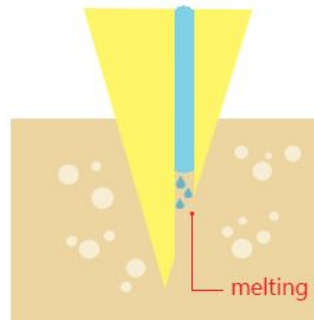
- Variations of Major idea #1
 - Patch on top of microneedle array (patch is directly on top of patch)



- Drug reservoir right on top of needles (i.e. no patch) and size controlling membrane
 - Problems: How can we actually put in things in this small drug reservoir?



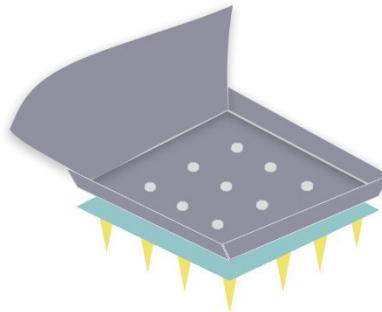
- Drug reservoir right on top of needles – media is initially frozen and then melted after application to body due to body heat
 - Problems: can't make the media frozen because expensive (buy refrigerator)
 - Frozen media will also expand like water, so when it melts it may not come into contact with spores



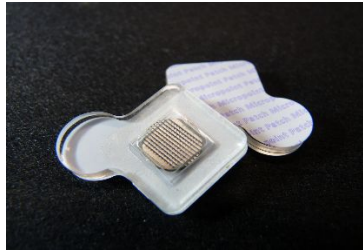
- 1 packet containing the bacteria in the drug reservoir → snap the packet to release bacteria spore
 - Problems: How can we actually put spores in small packets and then put them in the small drug reservoir? How can we break those packets?



- Introduction of a gel (on a “lid”/backing layer that is lowered onto the top of the microneedle array/drug reservoir) OR rate controlling membrane (hence we have a rate and size controlling membrane)
 - Problems: How do we put a lid on the top of the microneedle array? How do we stick the gel on the lid? If the gel falls, won't it block the size controlling membrane? How do we put a rate controlling membrane in the small microneedle array?



- *Major idea #2: Leave microneedle as it is; have larger patch that contains 2 chambers to separate LB and spores*



- backing material (what the block is made of)
- “valve”
- size controlling membrane
- adhesive layer
- microneedles

Constraints:

- 70 degrees C to activate spores
- Oxygen transmission: available (80-100 cc/m²/24h)

DR. DALTON'S MICRONEEDLES

- **Problem 1:** Geometry of microneedles
 - TIP:
 - Insertion force can be independent of the wall thickness
 - Fracture force increases with increasing wall thickness and increases with wall angle, also independent of tip radius
 - Side opened microneedles instead of standard tip microneedles – prevents tissue clog during insertion
 - High needle density can increase fluid flow rate

- Sharper needles require less force for insertion, but has reduce needle tip strength
 - Microneedle needs to be 10-15 um but shorter than 50-100 um to avoid pain
 - Best option: small tip radius, large wall thickness
- BODY:
 - Cylinder: eliminate stress concentrations, stronger needle structure, better self-adhesion
- **Problem 2:** Material for microneedles
 - Single crystalline silicon: high resistance to bending, can be fragile
 - Metal – greater strength, but thin metals are soft
- **Problem 3:** Application/removal
 - Application: Elastic nature of skin creates possibility of non-uniform contact of the array with the skin - an issue for correctly metering dosages
 - Has to find out which area of the skin where the least strain happens
 - Removal: Leakage when microneedle patch is removed
 - Development of microvalves within microneedles = passive system

Reference: Ashraf, M., Tayyaba, S., Nisar, A., Afzulpurkar, N., Bodhale, D., & Lomas, T. et al. (2010). Design, Fabrication and Analysis of Silicon Hollow Microneedles for Transdermal Drug Delivery System for Treatment of Hemodynamic Dysfunctions. *Cardiovascular Engineering*, 10(3), 91-108. <http://dx.doi.org/10.1007/s10558-010-9100-5>

MONDAY, MAY 9TH

FUTURE DESIGN TESTING:

- Test the proposed design with skin (animal skin?)
- Change diameter of hole - how much more different is the flow
- Heat of finger - enough to stimulate it?
- Diffusion works?
- Failure load (at what pressure does the needle break?)

STORAGE IDEA 1: FREEZE DRYING

- Order in microneedles > put in freezer > at temperature of freeze dry
 - If microneedles survive in the fridge, we should also test if diffusivity still works
 - If diffusion did not work, we have to look at pumps
- Membrane/Filter test: does the drug reservoir/peptide actually go through the filter? Does it prevent the bacteria from going through?
- Diffusion test: To test whether diffusion will actually work and what other problems we will face with diffusion (e.g. bacteria secretes peptides which go through the semipermeable membrane... but what about the media that goes through the membrane?)
- Making changes to the design
 - Is the drug reservoir actually contained properly in the microneedle?
- Bacteria test

MONDAY, MAY 16TH

EXPERIMENT TO SOMEHOW TEST THE IDEA:

Objective:

Tested the level of frozen H₂O in microneedle as it melts into a cup of H₂O (l)

Materials:

- 200 uL pipet tip
- Distilled H₂O
- 200 uL pipetter
- Freezer
- 300 uL H₂O
- Parafilm/tape
- Black sharpie
- Test tube rack

Procedure:

1. We used a pipet to take in 150 uL of distilled water in a pipet tip and taped the bottom with parafilm/tape. We marked the water level with a black sharpie.
2. Put the pipet tip in freezer and let the H₂O freeze (10:50 am - after lunch).
3. Put pipet tip (just the tip area) into test tube of 300 uL (2x the volume of water in the needle). Cap the top with parafilm.
4. Overtime, see whether amount of H₂O (l) goes back to original height.

Results/Observation:

After putting the frozen water in the distilled H₂O (l) test tube (at normal tap temperature), we put parafilm on top to mimic the microneedle being capped.

- H₂O melts extremely fast (this is without adding body heat) - melted within 1-2 minutes
- In actual microneedle, H₂O (s) will melt very fast due to body heat. Also, silicon vs. plastic tube
- After melting we noticed H₂O (l) level in needle is at a constant level (significantly lower than initial amount). Eg) doesn't go back to original level
- H₂O did expand, but not too significantly from initial observation, we think it won't affect/damage the needle tip

MONDAY, MAY 9TH

IDEA 2: POPPING IDEA

- Instead of pump, have a chamber with cells have a positive pressure already within it - have it sealed
- Capsule - look into the 2014 team
- Thinking about having water in the capsule, keep water in capsule, break it and everything gets hydrated
- Coating the microneedles with palmitic acid, we don't need to create another compartment
- For medical uses, need only single administration, would we need the bacteria there? Could dissolving microneedles work?

MONDAY, JUNE 6TH

Tentative Materials for Our Patch

Part of the patch	Material	Pros	Cons
<p>Backing Layer</p> <p>Purpose:</p> <p>provides structural support and protects the middle adhesive layer from the environment</p>	<p>3M CoTran™ 9722 Backing Polyethylene Monolayer Film</p> <p>Alternative: (2nd best out of 3)</p> <p>3M CoTran™ 9719 Backing Polyethylene Monolayer Film</p>	<p>Out of the three films 3M offers, the qualities that we thought would be beneficial are:</p> <ul style="list-style-type: none"> Elongation = for movement of patient, has to 600% elongation, highest of the three MVTR = this has the lowest amount out of all 3 <p>Translucent Breathable Printable Can be directly laminated to adhesives Heat Sealable (PE) Designed to resist excipient and drug uptake</p>	<p>We are not sure how much oxygen the bacteria would be using. We are not sure if 6400 cc/m²/day is enough for oxygen transmission.</p> <p>We do not know if this would turn cloudy after a period of time as currently existing patches with clear backing undergo the same issue.</p>
<p>Adhesive Layer</p> <p>Also note that thicker adhesive layer also results in severe cold flow during storage in the pouch, and higher affinity for lint and dirt to adhere to the edge of the patch during wear.</p>	<p>pdf of Duro-Tak Transdermal Adhesives</p>		
Release Liner	<p>3M Scotchpak 1022 3M Scotchpak 9741 3M Scotchpak 9742 3M Scotchpak 9744 3M Scotchpak 9755</p>	<ul style="list-style-type: none"> Good for release with silicon skin contact adhesives, acrylate, PIB and rubber based PSA Excellent chemical stability 	
Size-controlling membrane	tentative		

IMPORTANT NOTES

MONDAY, JUNE 20TH

- Emailed 3M for products, will talk to them tomorrow if they haven't replied.
 - Got a reply from 3M. Will need to call them later to ask for products.
- Emailed Dow Corning for adhesives
- Emailed Dr. Nezhad, an Electrical Engineering prof whose research is focused on microfluidics, for meeting
- Researched about different assays for material testing

MONDAY, JUNE 27TH

- Contacted 3M again, they are sending us the samples (YES). They should be here by the end of next week.
- Dow Corning will send the adhesives on 29th of June
- Today the device team focused on the math model for diffusion as weird numbers for the initial amount of peptides that needs to be produced have been calculated. Noshin found a paper with a MATLAB code that can be used to calculate the diffusion across a membrane using Fick's second law of diffusion. An email was sent out to Dr. Nygren to get his opinion on the code and see if we are heading in the right direction
- UPDATE: We meet with Dr. Nygren Wednesday to go over the mathematical model developed. He suggested in his email that the equation is applicable in principle, but the situation is a little different because the membrane and skin surface are probably the main diffusion barriers and the diffusion constant is (very) different at those barriers compared to everywhere else. He also suggest we create a numerical method rather than doing it analytically.

TUESDAY, JUNE 28TH

- The device group continued to work on both learning Solidworks to build the graphical model as well as the mathematical model of the diffusion of BBI through the patch, skin and into the bloodstream.
- From our results we calculated that we need 2 g of peptide being produced in the patch. This however is not feasible and needs to be reworked.

WEDNESDAY, JUNE 29TH

- Protocols Tiff and Dave talked about with Dan
 - Test how much media go through and if peptides go through; safety mechanism
 - Can we make dye as a qualitative or quantitative aspect of the assay?
 - How do we confirm peptides make it through?
 - Critical: make sure cells stay where they are, and peptides go through
 - There may be a big difference in terms of the diffusion constants depending on the volume, barriers, material
 - Dr. Nygren's suggestions
 - DRAW
 - Volumes separated by membranes

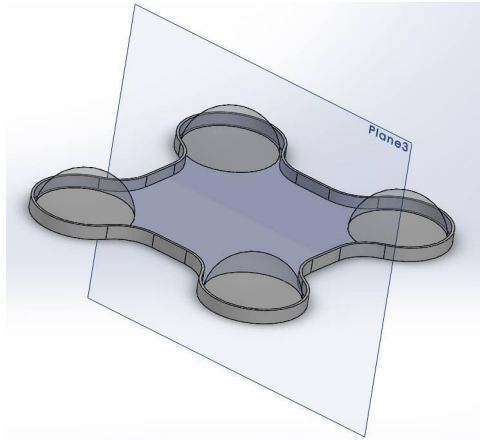
- Faster production = would reach steady state at some point as too much BBI might stop bacteria from producing
- Work equations out that he derived; make sure units are consistent
- Degradation - might be in the bloodstream, not before the skin
- Diffusion coefficients: testing would be necessary for peptide flow through membrane; for skin, could probably find from literature; or ask yourself, can we just find the diffusion coefficients rather than testing bunch of membranes?
- In our case diffusion is too fast that equilibrium is achievable.
- Make sure to state assumptions and a way to justify it.
- MATLAB: solving ODEs; recall ENGG 407 lecture

TUESDAY, JULY 5TH

- The rest of the team continued to work on the diffusion model based on Dr. Nygren's suggestions. Based on Noshin's work, there were too many unknowns that we could solve for if we decided to solve the equation as a function of time. Therefore we went back to Fick's first law where the diffusion was a function of concentration over area. This however had unknowns such as protein solubility that we weren't sure of
- Adhesive? Gave the green light that the assays are doable
 - Backing Layer? Gave a similar opinion that the assays are doable
 - Membrane? REASONABLE
 - Quantifying about how much peptide go through
 - Use of other peptides? (Since we want to quantify diffusion, maybe we could use something that is cheaper)
 - TRICKIEST: finding how much went through
 - Glucagon, oxytocin (20 - 30 amino acids long)

WEDNESDAY, JULY 13TH

- Contacted Dr. Nezhad about manufacturing patches, asked for resources.
- Contact Dr. Ingalls from Waterloo.
- Update: Waterloo is open for collaboration.
- In terms of modelling:
 - Had our equations sent to Brian Ingalls for checking.
- Christine developed the patch using SolidWorks! See below:



THURSDAY, JULY 14TH

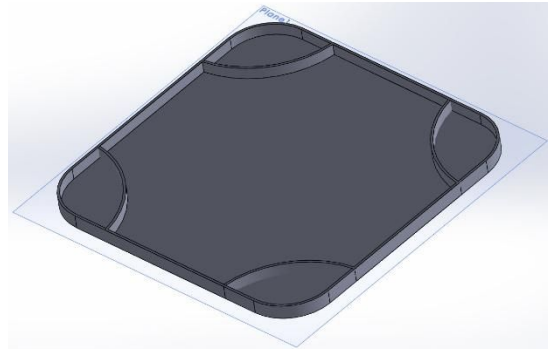
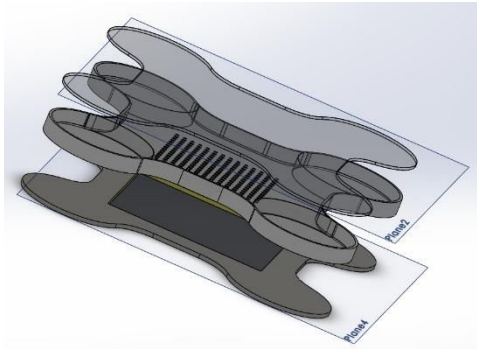
- Meeting with Dr. Sundararaj (UT) next thursday the 21st at CCIT 320 at 1 pm for manufacturing.
- Finished the analytical diffusion model across stratum corneum. See Device folder >> Patch Modelling >> open the only document there >> See Stratum corneum under Layer by Layer heading.
- Tiffany finished her initial models for the bottom layer of the patch
 - Optimized the dimensions to hold 10 mL in the main area, and either 0.5 and 1 mL of media in the pockets
 - Sent the models into 3D printing services at TFDL <3
 - Will hear back in a couple of business days about the progress

FRIDAY, JULY 15TH

Team Meeting

- Nelly has finished the first part of the analytical model for the stratum corneum. She will continue working on the next two parts of the analytical model for the next week
- Dave has been researching ways to manufacture to create the patch. For most industries including 3M they will only manufacture for large scale industry
- As a result Dave is focussing on how to manufacture our patch ourselves or with some professors
- Nelly will help out with Dave with this by researching into the adhesive and how to attach it
- Both Nelly and David have contacted professors for help in manufacturing the patch. We have a meeting with Dr. UT next Thursday at 1:00 pm with David, Nelly and Tiff
- If worse comes to worse and no one can help us, we are visiting the machine shop to see if anyone can help us
- Christine and Tiff have finished their prototypes. Tiff has sent hers to get 3D printed and will hear back in a couple of business days about the progress
- Christine and Tiff will start David's assay next week and run triplicates throughout the week to see if the patch growth curves matches the ones under optimal conditions already done in the lab
- Discussed with Nishi what needs to be done for mouse trials

- There are three trials being run: 6 mice for a positive and negative control, 6 mice with patches with BBI dissolved in DMSO, and 6 mice with patches with cell culture
- The patch is 1 cm X 1 cm X 0.2 cm
- The patches need to be completed Monday prior the experiments begin the following Monday
- Alina also messaged back Tiff to see how things were going
 - She will be escorting an astronaut from the Apollo 11 mission during a science fair and so we can send her questions we can ask the astronauts that will be there
 - Tiff will create a document for questions to send to Alina. Focus the questions on either radiation in space or their lifestyles in space
 - As well she said she will try to help us with our model. She said to message her as a group if we have questions about the diffusion model. Currently she is working on her own MATLAB project and she said could help us with this aspect specifically



TUESDAY, JULY 19TH

- This is what Nelly did for the whole day: [Check this out](#). She tried to organize all the models she had on file into a document. Hopefully it is easier to navigate in this format. She also uploaded all the codes, functions, scripts etc. She uploaded it in a folder under Patch Modelling.
- Followed up with Dr. Nezhad because he has not responded for 6 days.
- Finished first draft of the powerpoint about our project. Check *presentation under *device for it.
- Tiffany talked to Dr. Mayi concerning optimizing the diffusion assay
 - Instead of an eight hour interval of taking the sample, we will run the project over a seven day period, taking samples at 24 hour period to mimic the patch.
 - As well, we are now measuring the the optical densities over a spectrum as no literature points to a wavelength for saline solution/distilled water

WEDNESDAY, JULY 20TH

- Tiffany continued working on the diffusion assay and got initial results to determine the wavelength needed to determine the optical density of saline solution

- The falcon tubes containing LB, *B. subtilis* and *E.coli* were removed from the saline solution
- Saline solution was used as a blank
- Wavelengths of 260 nm, 300 nm, 600 nm, and 700 nm were used to measure the absorbance of the saline solutions contained in the erlenmeyer flask

WEDNESDAY, JULY 27TH

- Went to the machine shop to see if they can help us manufacture patches for prototype testing.
 - Although they were not super clear about what we wanted initially they figured out the basics of what we needed from them
 - They took care of 3D printing for free for us as we are a student based project and they resolved the issues for us
 - Tiffany is in contact with them and will hear back from them in a couple of days
 - In addition, we learned that the machine shop cannot manufacture the patch. What they do recommend is the easiest way would be to proceed with something similar to the thermoforming method
- About the thermofolding method
 - Suggested we cast a mold that they can help us design using metal. The mold would consist of two parts for the backing layer and the semipermeable membrane
 - We would then heat our materials and lay them onto the molds to conform to their shape. From there we place the molds together and inject our media into the mold and heat seal the entire patch together
 - Unfortunately they can only help us with the mold. They don't have equipment we could use
- We're gonna talk to Dr. Mayi/Nygren before we proceed to see if this is a good idea and how we can proceed about thermoforming.
- We also need to determine experimentally at what temperature we get the two materials to seal together. This has to be determined ourselves
- Tiff will bring hair iron + blow dryer tomorrow to test at what temperature we can heat seal our materials

THURSDAY, JULY 28TH

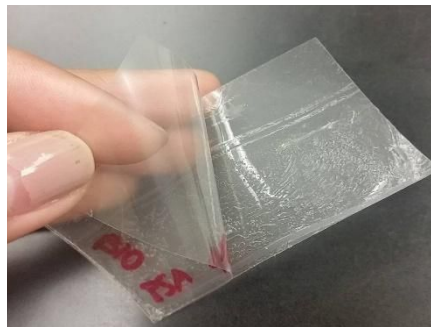
- The device team made prototypes today!
 - We used the flat iron, iron, and blow dryer. Iron worked best. See pic below!



- Nelly worked on her adhesives. She tested BIO-PSA 7-4101 and 7-4301; however, both tests failed. What she did on her first test was she applied a thin film of adhesive on the release liner and let the heptane evaporate. She waited for 20 minutes, but the adhesive dried completely that it lost its adhesive properties. She tried the second time and she waited for heptane to evaporate for 5 minutes. The adhesives still contained heptane. She would run tests again tomorrow for 10 and 15 minutes.

FRIDAY, JULY 29TH

- Had our weekly meeting. See timeline for what we have to accomplish next week.
- David contacted 3M to ask them to create a crude prototype so we have a better idea what the patch should look like.
- Nelly did rounds of her adhesive testing assays. She found that the BIO-PSA 7-4201 will be the best adhesive for our current purposes. BIO PSA 7-4101 dries up quickly as when it was applied, it lost its adhesiveness. BIO PSA 7-4301, on the other hand, dries up very slowly, which also explained why it is less viscous than the other adhesives. This means it is dissolved in more heptane. In the pic below, Nelly was holding onto the release liner, the other layer was our membrane. The adhesive was successfully stuck to the membrane.
 - Recommendations:
 - Use of rolling pin for more uniform adhesive distribution.
 - Wait 1.5 minutes for the adhesive to dry up once spread as film before attaching the membrane.
 - Test on pork skin. Design assays for quantifying amounts of adhesive we need to apply, optimal temperature for drying, etc.
 - More prototypes next week!

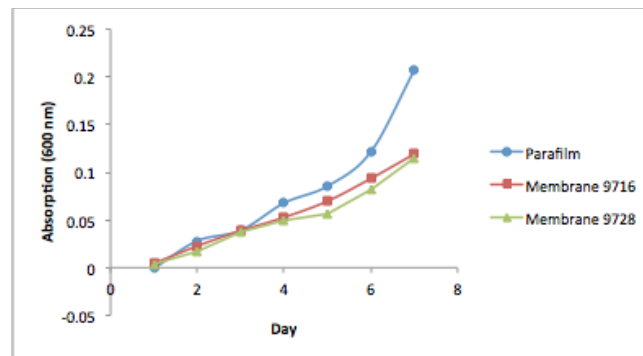
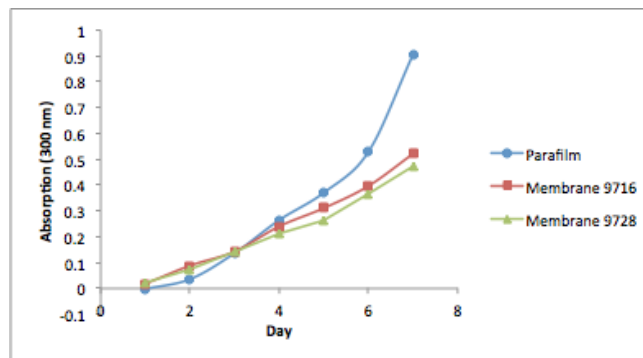
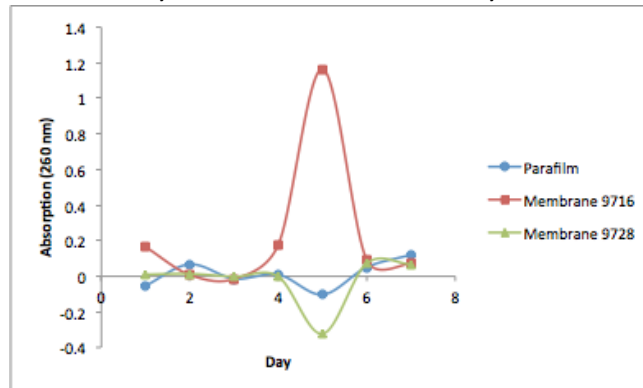


TUESDAY, AUGUST 2ND

- David finished a detailed word doc outline of the presentation (with some help from Nelly and Tiff <3). Check under Presentation folder and edit anything you'd like. Now pass on to Christine to create powerpoint. Christine started a rough draft of our presentation.
- In the lab
 - Tiff finished the last day of the diffusion assay
 - Nelly and David performed some adhesive experiments. They experienced problems and they are as follow:
 - The adhesive did not stick to the liner completely
 - Uneven distribution of adhesive on liner

WEDNESDAY, AUGUST 3RD

- Christine did the data analysis for the diffusion assay



- Nelly and David are testing adhesive. There were different methods used in doing these tests. They are as follow:
 - Rolling pin test**
 - An amount of adhesive was applied to the release liner.
 - A cut out of EVA membrane was placed onto the adhesive.
 - Place another layer of the release liner on the membrane to prevent the adhesives from sticking to the rolling pin.
 - Roll the pin on the layer to distribute adhesive.
 - Let it dry.
 - Film application test**
 - An amount of adhesive was applied to the release liner. The adhesive must be applied I a straight line.

- i. Spread the adhesive using a popsicle stick to form a thin film.
 - ii. Wait for a minute before placing a cut out of EVA membrane onto the release liner to dry
- b. Two - release - liner - sandwiched - together test**

An amount of adhesive was applied to the release liner. The adhesive must be applied in a spiral manner.

 - i. Place another layer of the release liner onto the initial liner.
 - ii. Spread the adhesive using a rolling pin, by pressing, etc. until you see a clear film (meaning, no air bubbles, no accumulated glue anywhere, etc.)
 - iii. Wait for 20 minutes to let the adhesives settle for a bit.
 - iv. Peel the liners apart.
 - v. Place a cutout of the EVA membrane onto the liner.
 - vi. Let it dry.

Results from the adhesive tests:

- a. Rolling pin test: Opposite to what was expected, the adhesives were unevenly distributed. Air bubbles and bumps of glue were present. Some had not completely dried up, forming webs when peeled, some had.
- b. Film application test: The adhesives were unevenly distributed.
- c. Two - release - liner - sandwiched - together test: The adhesives were unevenly distributed, but this method was the most effective one. See pic below!



- Tiffany also picked up the 3D printed models of our prototype from the machine shop



THURSDAY, AUGUST 4TH

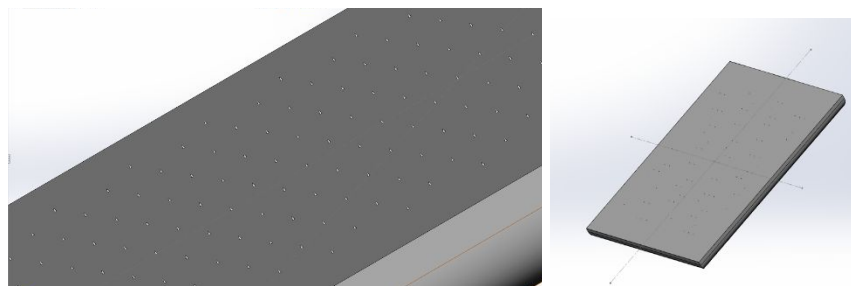
Team had a meeting with Dr. Nygren

- Updates
 - 3D printing
 - Patch seemed to be a reasonable size according to Dr. Nygren

- Diffusion assays
 - There were bacteria leakage that happened
 - Back up plans, solving issues
- Meeting with Dr. UT
 - Thermoforming
- Prototyping
 - Maybe we could use wax paper or parchment paper. See what happens.
 - Machine shop may not be able to help us since they will be closing soon for renovations. They would require us to send the SolidWorks model asap. They can't do heat sealing for us, but they can make the mould.
 - For the mould: instead of making 18 patches at a time, make it simple by making 1 at a time. Easier to manufacture, cheaper
 - Adhesive: use of heat
- Manufacturing
 - Materials for moulding
 - Suggestions he could give us
 - Moulding design he could provide
 - One at a time
 - Contacts for manufacturing
 - Companies: nope
 - Professors: nope
- Modelling
 - Diffusion model Noshin prepared
 - MATLAB code
 - ODE45 will help us get numerical values instead of having a function as a solution
 - C_2 degradation
 - Flux = moles/(m². s); production rate = moles/s
 - Start with assumed values for production rate and then move forward.
 - Diffusion model Nelly prepared
 - Will send the document to Dr. Nygren for checking

FRIDAY, AUGUST 5TH

- Mason completed a SolidWorks model of a previous microneedle prototype design
- Noshin and David continued to manufacture patches in the lab. Following Nelly's procedure, they made patches that were 1 cm x 1 cm



MONDAY, AUGUST 8TH

- Tiffany and Christine planned the week to perform the backing layer growth curves. These growth curves will be used to determine if cell growth is affected when gas exchange is limited
 - The Plan
 - Tuesday start the overnight cultures for the growth curves in the falcon tubes
 - Wednesday at 4:00 pm, 12:00 and Thursday at 8:00 am start inoculation for the tubes
 - Thursday start overnight cultures for the growth curves in the patch and perform growth curves for falcon tubes
 - Perform growth curves in the patch
 - Before starting the growth curves in the patch, soak the 3D printed models in 70% ethanol overnight

TUESDAY, AUGUST 9TH

- Tiffany started the overnight cultures for the growth curves in the falcon tubes
- Nelly and David made patch prototypes today. The procedures are as follows:

Materials:

- Strips of release liner (5cm x 13.2 cm)
- Strips of EVA membrane (5cm x 13.2 cm)
- Square cut outs of backing layer
- BIO PSA adhesive
- Cylindrical metal bar
- Masking tape
- Scissors, marker, ruler
- Flat plastic surface
- Iron
- Syringe + needle

Procedures:

A. Preparation of the adhesive layer

1. Have the materials ready. Perform the process under the fume hood as the adhesives contain heptane. Heptane is flammable and create vapor trails that may cause fire.
2. Note that the coated side of the liner is where the adhesive will be applied. In case you cannot figure which one is the right side, grab a marker and try to write on both sides of the liner. If the ink stayed permanently on the liner, you wrote on the uncoated side. The side where the ink just slipped through would be the coated side. It would be recommended to write which side is which to avoid confusion.
3. Draw a horizontal line on one end of the release liners (1cm from the end) with a marker. This end will be taped to keep the liner in place when the adhesive is being applied.
4. Draw three 3cm x 3cm squares on the release liners. Make sure to leave ample amount of space between the squares. Draw 1cm x 1cm squares inside the initial squares.

5. Take all the materials under the fume hood. Tape the end release liner on the flat plastic surface.
6. Apply the adhesive on the line initially drawn. Apply a constant pea-size amount on the line.
7. Using the metal bar, spread the adhesive onto the liner. Spreading using a metal bar will form a thin film of adhesive on the liner.
8. Wait for about a minute before placing the EVA on the layer.
9. Carefully place the EVA membrane strip on the adhesive layer.
10. Lightly tap the membrane to stick.
11. Wait for the adhesive to completely dry (1 hr - 3 hrs).
12. Cut out the squares.

B. Heat sealing the patch

1. Set the iron to the heat sealing temperature that was previously determined.
2. Place the backing layer on the prepared adhesive-membrane layer.
3. Carefully iron the sides of the layer. Avoid ironing parts of the 1cm x 1cm square centre drawn. This is where the nutrient rich media and bacteria will be stored.

C. Adding the media in

1. Obtain the required amount/volume of media to be stored in the patch using a syringe.
2. Carefully inject the media into the middle compartments of the prepared patches by poking a hole on one of the corners of the drawn center squares.
3. Heat seal the holes created by the needles.

***Check the whole document under https://docs.google.com/document/d/18uXLyuw3K3-0EAXaxPTyErA_iBWKPDveNloJplzlsIU/edit

WEDNESDAY, AUGUST 10TH

- The team went to the Foothills machine shop yesterday at around 2pm to consult with Peter Byrne. He was the person Dr. Nygren had referred during our last meeting. We had set the mould specifications for him to follow. He had also given us suggestions to further improve our mould. The mould will be ready for about a week. (\$50 per hour of labour by the way ladies and gentlemen).
 - The mould will be made with aluminum and brass that may stick to our layers. He then recommended us to get a Teflon coating spray or something the same.
- Nelly finished adding her Powerpoint slides for the presentation on Monday. She also picked up a Dupont Non-stick Lubricant (with Teflon) from Canadian Tire.
- David and Nelly made more adhesive layers before leaving the lab. Some had thicker adhesives applied, some had thinner layers. They will see how this quality would affect adhesion or if it has any effect at all.
- Nelly tried one of the adhesive layer on her wrist. It took her a while to completely stick the layer on because it had thin adhesive coating. It also required applied pressure for it stick better. She had the layer on for 4 hours.
 - Result: The layer was somehow painful to remove because some of her hair were stuck on the adhesive. She said the pain felt like a degree lower than a

wax sheet slowly being peeled off your skin. There was no redness or irritation that happened on her skin, but itchiness was felt when the layer was on.

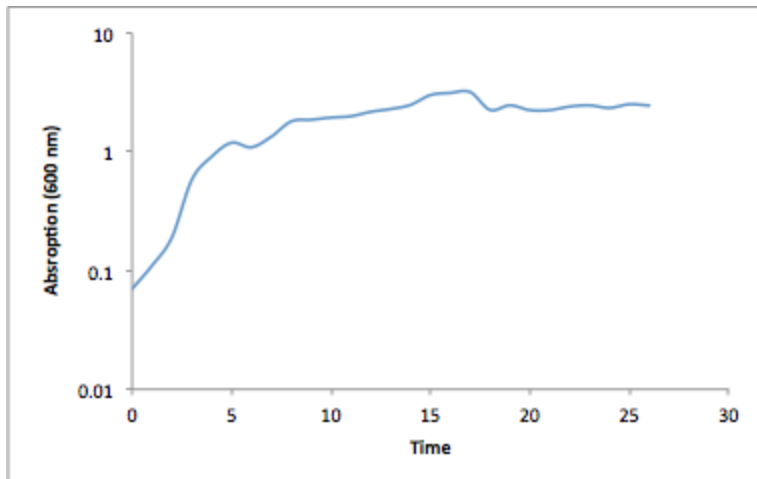
- Recommendations: Disinfect the skin area before patch application.
- Christine continued working on the animation for Maya today and edited our presentation for August 15th.
- Tiffany conducted assays in the laboratory today
- Tiffany had also tested in the lab if the 3D models would hold the initially calculated volume of media.
 - Results: The pockets exactly held 0.5 mL of liquid, while the content area held exactly 10 mL. Therefore, the 3D model is a good representation of our patch system in terms of holding capacity.

THURSDAY, AUGUST 11TH

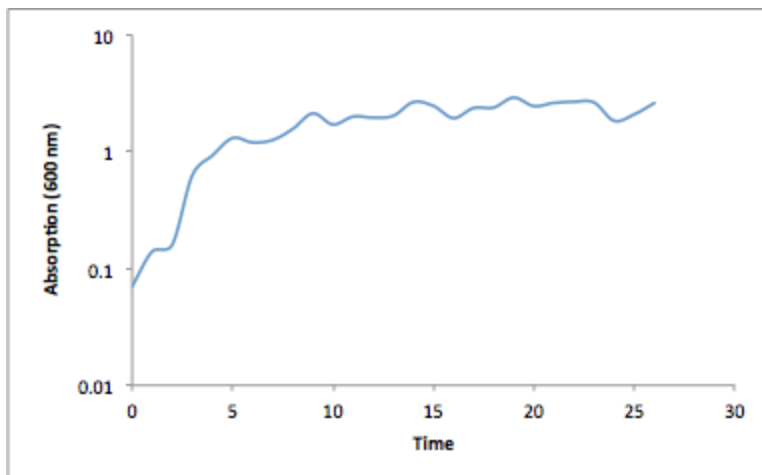
- Tiffany's focus today was to conduct the growth curve assays every 40 minutes.
- Meeting with Dr. Nygren
 - Potential questions here → [Questions for Dr. Nygren document](#)
- Meeting minutes:
 - Update:
 - Showed Dr. Nygren the full system prototype Nelly and David made
 - Continuing assays by Tiffany and Christine
 - Christine is working on her video
 - Noshin is working on her math model
 - Went to machine shop to get the thermoforming mold done
 - Modelling:
 - Dr. Nygren said Noshin is on the right track. He will email her to clarify some details.
 - Prototyping:
 - Dr. Nygren suggested talking to Dr. Jenne about the prototype and alter it to better suit the mice.
 - Ask Dr. Mayi to buy the heat gun on our own
 - Assays:
 - Try to make a connection between the assays and math models. Answer the question of why we do the assay, why we have the models, what the connections are. Cohesion is key.

FRIDAY, AUGUST 12TH

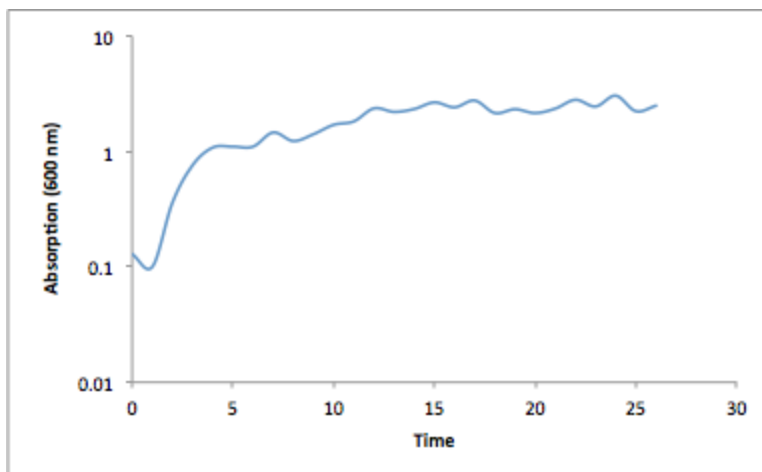
- Christine and Tiffany worked on entering data values of their growth curve assays in a spreadsheet. They created time versus absorption plots.
 - Results:
Tube 1



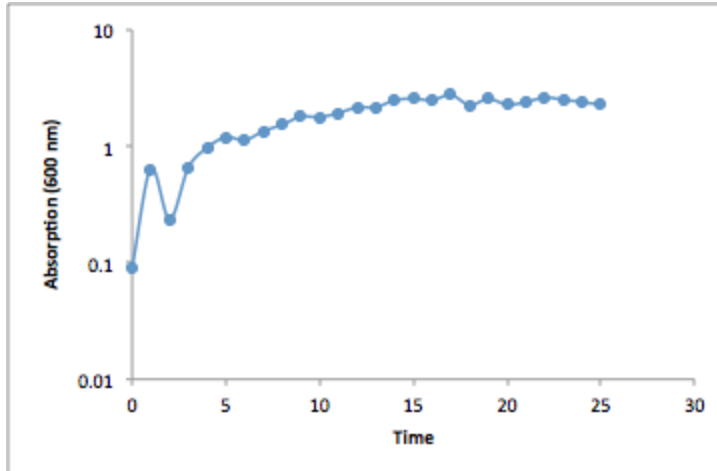
Tube 2



Tube 3



Average of Tube 1, 2 & 3



MONDAY, AUGUST 15TH

- Presentation day! What we basically did for today was preparing for our presentation and did run throughs.
- After the presentation: dead. There were challenging questions thrown at us. This means we still have things to be solidified before we can say we're done.
- We also asked our mentors for comments with regards to our presentation. They are as follows:
 - Instead of having a slide with all equations on them, why not just use words that tells our audience what the terms represent.
 - Maya animation. Changes to be made could be:
 - Making the adhesive liner take up the whole bottom area of the patch.
 - We're not using the indicator system to signal low media, but tells if the bacteria is activated.
 - After we have shown how the patch works, we can also extend the story by, say, an astronaut peels off the liner and apply patch, then wears this for this how many hours, and then through our modelling results we'll figure how long before we pop a packet and then what would happen next and, you know, the story goes on yadi yadi yada.
 - Our graphs must be able to speak for themselves, meaning that by the time we look at them, we know right away what it is trying to tell us.
 - Explain all the terms that we are talking about.
 - CONNECT ALL THINGS TOGETHER.
 - Use constants that are from the other teams. The values we get from our model runs must correlate to the models and numbers Chassis and Biotarget get. Both Rai and Dr. Nygren brought this up.
 - Our model should also have a flow.

FRIDAY, AUGUST 19TH

- David and Nelly made more adhesive laminates, preparing for more prototypes

TUESDAY, AUGUST 23RD

- Tiffany continued doing her diffusion assays. The dialysis membranes came today as well and treated for testing. There were two types of tubing membranes that were used: 20 kD and 628 kD pore size membranes. However, these membranes are not heat sealable which would be a problem in manufacturing. There were other limitations that were mentioned and these can be found in the email Nilesh sent/cc'd us in. Tiffany will be performing diffusion assays for these membranes tomorrow.
 - Must be soaked in room temperature distilled water for 30 minutes instead of being boiled
 - "Just soak them- once you have figured out how to glue them together" -- Dr. Volgo
- Nelly made around 80 adhesive laminates.

WEDNESDAY, AUGUST 24TH

- Tiffany performed her diffusion assays experiment using the dialysis tubing membranes.
- Noshin worked on modelling and sent the codes to Dr. Nygren for checking.
 - She also asked Dr. Nygren if he could give us a contact who could help us with cost analysis for our patch.

FRIDAY, AUGUST 26TH

- Tiffany and Christine picked up the moulds from the Foothills machine shop.
- The results from dialysis membrane diffusion assays came out. There is still diffusion of bacteria through the membrane.
- The team also met with a PhD scholar, Xiaolan Li, whose research project focuses on water filtration using nanoporous membranes. Robert, a student who works in Li's lab, is also in the meeting.

CHANGING POINTS IN OUR PROJECT

MONDAY, MAY 30TH

MEETING WITH DR. DALTON:

- Contact 3M for hollow microneedles, look at patents
- If he can find his microneedles he will give it to us
- Would have to consider shear stress, what if microneedles break off and go into the body
- Utah array - solid microneedle
- Lab on a chip - chips and tips
- Perhaps make microneedle system separate with valve
- Issues:
 - In microfluidic systems are bubbles - bubble will block channels
 - LB chamber, what's stopping the fluid from flowing directly out the microneedles? Perhaps use a mechanical system to control pressure, could also suck the media back in
 - Diffusion would be way too slow or not even occur, would need an external syringe pump
 - Leaving microneedles in for too long will cause immune response from body, wound infections
 - Need to determine how much pressure the membrane can take
 - Consider stress on microneedles, fact that skin is very mobile
 - Skin elasticity, skin varies by thickness based on ethnicity and age, also have to consider the hairs on the skin

WEDNESDAY, JUNE 22ND

- Meeting with Dr. Amir Nezhad
 - About Dr. Amir Nezhad's Research
 - Dr. Sanati-Nezhad' primary research interest involves BioMEMS, Microfluidics, Tissue Engineering, Micro and Nano Technology, and Lab-on-Chip.
 - His research group has focus on development of integrated bioinspired microdevices using microfluidics and tissue engineering approaches for disease modeling, biological systems modeling, and drug discovery.
 - Another research interest of his group is to develop point-of-care devices for testing infectious diseases, and portable tools for detection of plant and food pathogens.
 - On meeting with him, we were invited to his lab where he showed us the process of micro fabricating the labs on the chips and how he uses microfluidics in order to do so
 - The fabrication process is difficult. It requires a semi permeable membrane in the middle where the individual cells can be housed.
 - Surrounding the permeable membrane is silicone mold to provide structure and handling.

- Although the chip looks simple, actual analysis requires a system of micropumps to transfer media, waste and byproducts across the system. This in turn is connected to a computer or microscope system for analysis.
- In order to work for cells for 30 days, the first 6 - 15 days is incubating the cells and ensuring they are in a happy media. After that, you can start researching on the cells
- He mentioned the importance of finding the optimal flow rate in the chip because anything above or below they flow, will disrupt the cells and kill them
- In concerns with our project
 - He thinks the general idea of a patch system releasing various peptides into the body is very interesting and sees potential for collaboration with his lab
 - When asked about companies to order from he suggested Dow Corning
 - He stressed the importance of drafting up a prototype of our design in AutoCAD so he could better understand what our design will look like (not really? We asked him what he used for visual modelling and he said AutoCAD. However, he did stress making a powerpoint presentation to show people we consult to give them a better idea of what we are doing)
 - Gave us access from his lab to purchase AutoCAD
 - When asked about fabrication, he volunteered his services or that of the mechanical shop to create a prototype

THURSDAY, JUNE 23RD

Meeting with Dan and Dr. Mayi

- Contacted Porex for EVA samples - waiting for response
- Also discussed with Dan about assays we can perform for both the semi permeable membrane and backing layer
 - For the semi permeable membrane
 - Using a 15 mL falcon tube, we can fill it with overnight cultures and wrap the semi permeable membrane underneath the lid. We then invert it in a larger 50 mL falcon tube with water, salts and at the same pH as the blood and leave it to sit. After hourly intervals, we would take samples of the water and take the OD readings.
 - Another assay that we can do is to use a brute force method and apply the same setup as the first assay. However we would centrifuge it down and see at the extremes how well our semi permeable membrane works.
 - For the backing layer
 - Dr. Mayi suggested creating a small patch with overnight cultures and leave it to sit in conditions similar to those found in the ISS. We take an OD reading initially and then let it sit for eight hours before taking another reading at the end and comparing the growth of our cells. We can also measure the amount of moisture vapour by measuring before and after the mass of the patch.
 - Dan also suggested something similar to measure how well our cells grow. Using the small plates, we would aliquot some of our overnight cultures into two plates.

We would then cover one with parafilm and the other with our backing layer. We then leave them to shake in the incubator. We take the initial OD and the final OD reading then of both to see how well our cells have grown

THURSDAY, JULY 21TH

- David replied to 3M, they sent me back an email with useful info. I forwarded to everyone:
 - Temperature and pressure depends on system:
 - 250F and 40 psi for their small single well sealer - 1 second so the liner doesn't warp.
 - However, multiple well sealer needs 300F, 50 psi
 - => May need a few trials to decide the parameters
 - They can create a crude prototype to give us some idea of usability
 - If making it ourselves, they recommend a sequence of steps:
 - coat adhesive onto the liner, laminate the membrane to the liner through a low pressure nip roller and lastly heat seal the backing to the lamination (on the membrane side) by placing the materials to be sealed onto a well type receiving fixture with silicone sealing gaskets and using a platen type seal plate above.
 - Our membranes are the most permeable. The main difference is the thickness between the 2. The thicker one (9716) will have a slower transmission rate. If nothing works, they'll help us pick out another one.
- Meeting with Dr. UT Sundararaj about manufacturing:
 - He went over the project with us and said gel media might be safer when being punctured but diffusion might be compromised. However, he said at equilibrium everything should be the same.
 - He approved our materials for the patch. He told us to consider the materials' solubility parameters to make sure they are compatible and nothing will dissolve into each other when heated. EVA and polyethylene are fine. We might want to check hexane/heptane in the silicone adhesive and EVA though, but it should be fine.
 - <http://cool.conservation-us.org/byauth/burke/solpar/solpar2.html> If delta is >+-2 it should be okay.
 - He recommended using thermoforming for our mouse patches. The general idea is to make a wood "mold", heat our backing layer up, put it on, vacuum so it forms a reservoir, pour the media in, put the membrane on top, and then heat seal everything together. A flat iron for hair or something might work. It's also a good idea to apply heat on both sides.
 - Thus, we need to get in touch with the machine shop ASAP <http://www.plasticmag.com/thermoforming.asp?flssue=Mar/Apr-03> some reference we pulled out from google today about thermoforming.

FRIDAY, JULY 22ND

- Dow Corning (finally!) responded to Nelly about the preparation of adhesives.
 - Basically, the actual adhesives are dissolved in heptane. This is the reason why handling it without precaution might cause irritation. The adhesive in its pure form is safe to use.

- Easy enough, we just have to let the heptane evaporate so we can use the adhesives. The evaporation rate will depend on the temperature of the environment. In some patent documents she found online, companies dried the same type of adhesive in 100°C oven for 2-3 minutes.
- Note, we must do any adhesive assays under the fume hood.

WEDNESDAY, AUGUST 17TH

- Meeting with Dr. Jenne (August 17, 2016)
 - Mouse orders done on Wed the 24th potentially
 - Might take some time to do training, he's concerned about the timeline since he technically can't order mice until he got ethics done
 - He thinks that the biggest thing for us is mass spectrometry
 - Problems we might encounter:
 - Peptide not being found in the blood
 - If it's found in the blood, what if it's absorbed by other cells or organs
 - The most important thing is what we get out of it, what the results tell us, and our future solutions for it. It's okay if it fails.
- We have to change the dimensions of our patch to make it narrower and longer.

MONDAY, AUGUST 22ND

- Modelling meeting with Dan
 - In our modelling story, this experiment would be in the beginning of the story. This would be use which peptide we are going to use. Once our peptide has gone into the bloodstream, this model would help us determine how fast our peptides would diffuse through the cells to do its functions.
 - Different forms of our peptide
 - How it would go through our membrane
 - Looking at the energy levels
 - Applying force to membrane through a bilayer
 - Very hydrophobic = low energy in the middle
 - Calculate energy
 - Size of the system
 - Peptides: we want to model the different forms of our peptide and see which diffuse the fastest
 - 9-residue monomer - linear (reduced form) and cyclic (oxidized form, ring, forming a disulfide bond = might affect diffusion, should it be reduced or not)
 - TD1 tag: compare that to BBI (combination of the 2 may have a better effect)
 - KSCI + monomer + F at the end
 - Having a negative control
 - Like a sodium ion (+ve)
 - Hormone that readily diffuses through
 - Another important part: bilayer
 - Simulate the actual membrane

- One type of human bilayer = have a smoother curve
- Or a hydrocarbon bilayer/disc
- Talk to them if we could have a simple bilayer with true phospholipid
- Explicit water on the outside
- Size of the environment (10nm cube, etc.)
- Ask if there is data already existing

FRIDAY, AUGUST 26TH

- The team also met with a PhD scholar, Xiaolan Li, whose research project focuses on water filtration using nanoporous membranes. Robert, a student who works in Li's lab, is also in the meeting. He was a previous member of the winning iGEM team in 201_. Here's what we talked about:
 - Ask Dr. Mayi or Deirdre about other membranes that we could test
 - Examples
 - centricon: small scale version, 5kD (ask Goodarzi's godmother): not as big, small scale purification, good for centrifuge works
 - filter sterilization membranes (0.22 micron)
 - Watch 2011 NASA - video
 - figure out what carbon nanotubes we need, they got some. They have PPL, carbon nanotubes. Once we've tried everything and still fail, then we should ask them.
 - Other ideas
 - dissolving O₂ on the actual membrane
 - We need less than 200 nm of pore sizes
 - SEM, AFM: contact Matthias Amrein - does lung cells; Michael (runs SEM)
 - use something conductive, Teflon is not conductive
 - thin sheet of gold
 - figure out what materials we would need at the moment

PROVIDERS

COMPANIES INVOLVED:

3M

- Provided us with all the sample materials used in the team's assays
- The following materials are as follows:
 - 3M CoTran™ 9722 Backing Polyethylene Monolayer Film
 - 3M CoTran™ 9719 Backing Polyethylene Monolayer Film
 - 3M CoTran™ 9716 Ethylene Vinyl Acetate Membrane
 - 3M CoTran™ 9728 Ethylene Vinyl Acetate Membrane
 - 3M Scotchpak™ 1022 Release Liner Fluoropolymer Coated Polyester Film

Dow CORNING

- Provides us with the adhesive samples used in our patches.
- The following materials are as follows:
 - Dow Corning BIO-PSA Silicone-based Adhesive 7-4101
 - Dow Corning BIO-PSA Silicone-based Adhesive 7-4201
 - Dow Corning BIO-PSA Silicone-based Adhesive 7-4301

COLLABORATIONS

THURSDAY, JULY 7TH

- The team continued working on the diffusion model by either researching the equations further to see if there is another perspective we can take on the model or writing a code that can be used in MATLAB
- Nelly was able to get a graph of the result of her MATLAB code [Insert image or comments here about the result Nelly!]
- Meeting with Waterloo
 - The modelling team met with the UWaterloo Modelling leads to discuss a possibility for collaboration
 - They are working on a project that uses yeast to take advantage of the higher readthrough rates during prion response
 - There is not very much commonality between the two projects but one potential would be a collaboration on their protein aggregation model as it would involve transcription rates
 - However after discussing, it may not be worth the collaboration between us and Waterloo

iGEM COLLABORATION UCALGARY & UWATERLOO MM

07 JULY 2016 / 4:00 PM

ATTENDEES

- Zoë Humphries, Emily Watson, Tiffany Dang, Nelly Mendoza, David Nguyen, Sid Goutam and Nilesh Sharma

BRIEF INTRO

UWaterloo Project Summary

- Creating a system that takes advantage of higher readthrough rates during [PSI+] state of prion response
- Model of iGEM collaboration network from 2015
- Model of plasmid retention - metabolic load of expressing our fusion protein
- Model of protein aggregation - how the prions are distributed through generations

UCalgary Project Summary

- Working a transdermal delivery system to deliver peptides to the body
- Specifically working on the delivery of the Bowman Birk Inhibitor which as shown radioprotective effects
- Modelling the diffusion of BBI into the body to determine the initial concentration needed to be produced
- Model of the required transcription rates to produce the required amount of BBI or what a reasonable amount of BBI can be expected

MORE DETAIL ABOUT WATERLOO MODEL

- Gene Retention Model
- Determine number of copies based on fluorescent protein in plasmids
- Retention is dependent on metabolic load, stability of plasmid,

- Quantify using fluorimetry
- Protein Aggregation Model
- Model how long it takes for aggregation to form (help lab subteam)
- No differential equations as of yet
- Probabilistics important for chance of inheritance in daughter cells
- Quantify aggregation via Western blots
- System should break down prions, will model this disassembly
- Quantify breakdown via GFP (sup35 prion protein begins functioning again)

MORE DETAIL ABOUT CALGARY MODEL

- Diffusion Model
- Model how long it takes for the diffusion of BBI to reach steady state
- Compartmentalized the diffusion system into three components: the patch to the skin to the blood stream
- No differentials equations at this point but trying to use Fick's Law in MATLAB to see if we can analytically solve for the steady state
- Also using this model to determine the initial concentration needed in the patch for the desired amount of BBI to be found in the blood stream
- Transcription Rate Model
- Model to determine how fast the peptides are being produced inside the patch and how varying transcription rates will create the necessary concentration of peptide needed in the patch

ACTUAL ITEMS FOR COLLABORATION

UCalgary Assistance

- Help starting with the transcription rate models to determine how fast the peptides are being produced and what is a reasonable initial concentration based on these rates
- Mentoring for the diffusion model. This would be in the form of bouncing questions with Waterloo to see if we are on the right track and if there are any considerations we need to take
- With the gene retention model, UCalgary can help by collaborating on the transcription rates specifically

UWaterloo Assistance

- Gene retention subgroup most likely to benefit from assistance
- Optimising expression of plasmid number over gene copy number in plasmid
- Modelling expression of gene, how quickly the plasmid is lost during normal and prion states ([PSI⁺] condition)
- Dr. Brian Ingalls works on gene retention in bacteria, is a great resource
- Transcription rates would benefit gene retention and protein aggregation

ACTION ITEMS

- Use Google Drive to maintain collaboration docs
- UWaterloo will send update e-mail to math subteam & CC UCalgary

MANUFACTURING

WEDNESDAY, AUGUST 24TH

- Dave and Nel worked on manufacturing today. David had figure out a way to properly make our mice testing patches. The protocol is as follows:

Procedure:

1. Prepare the adhesive laminates following Nelly's procedure
2. Plug the iron in to preheat.
3. Look through the adhesive laminate under a light source and pick out and most even area. Sketch the 1 x 1 cm square on the liner at the center of the area
4. Trim the laminate to roughly 1.5 x 1.5 cm
5. Lay the laminate membrane-side up on the iron board, and the backing layer on top
6. Iron 1 side of the patch up to the sketch. To make the seal even and bubble free, when sealing, apply more pressure on the side of the iron that's touching the line, then tilt the iron so that side of the iron lifts up slightly, then press it down again, after each time, move the iron away from the line to the edge of the patch. The seal should look clearer than the center. If not, then the iron is not hot enough, redo using a different side of the iron until it's clear
7. Seal the other 3 edges. Now the patch should be stuck to the iron board, leave it there. Repeat the process for another 2 patches.
8. Remove the first patch from the iron board. Prevent peeling the patch off the liner by sliding a finger under the patch after you peel off 1 corner when you reach the liner.
9. Hold the patch diagonally, vertically, backing-side facing you. Bend it slightly so the backing folds towards you. The backing at the center (not sealed) should bend and separate from the membrane, creating a thin pocket running diagonally from the top corner to the bottom corner.
10. Fill the syringe with water, use the needle to poke a hole at the top corner of the patch, make sure the needle did not poke anywhere else and the needle is in deeper than half of the patch.
11. Inject the water slowly, keep a bend in the patch so we have a pocket, fill it from the bottom corner, tilt the needle and the patch to get the other 2 corners, then fill it nearly to the top corner. A good volume should be 0.06 - 0.08 mL
12. Remove the needle straight out, a drop of water may leak out, dry it lightly with paper towel, don't push on it
13. Lay it on the iron board. Make sure there's no water droplet visible. If there is, dry it gently with a paper towel, then iron on the hole for about 1-2 seconds
14. Press on the patch slightly to see if there's still any leaks, if yes, dry the droplet of water with paper towel and re-iron the corner until there's no more leaks.
15. Now the patch is done, trim the sealed sides with scissors to approximately half of the original side dimensions. Round off the sharp corners

16. Cut a bandage in half, horizontally, then cut it vertically to create 2 small rectangles, with the sides approximately to be twice of the sealed sides of the patch
17. To put the patch on a finger, remove the liner, put it on and press all edges lightly but firmly until all edges stay down
18. To reinforce the patch, put the 2 bandage pieces on both sides that go down to the sides of the finger

***Note:** A patch with “YES” written on it is on the iron board. It should show you the size of the patch, how clear the seals get, and how I seal the hole. You can ask Tiffany about the process of applying since she had 5 on her fingers today.

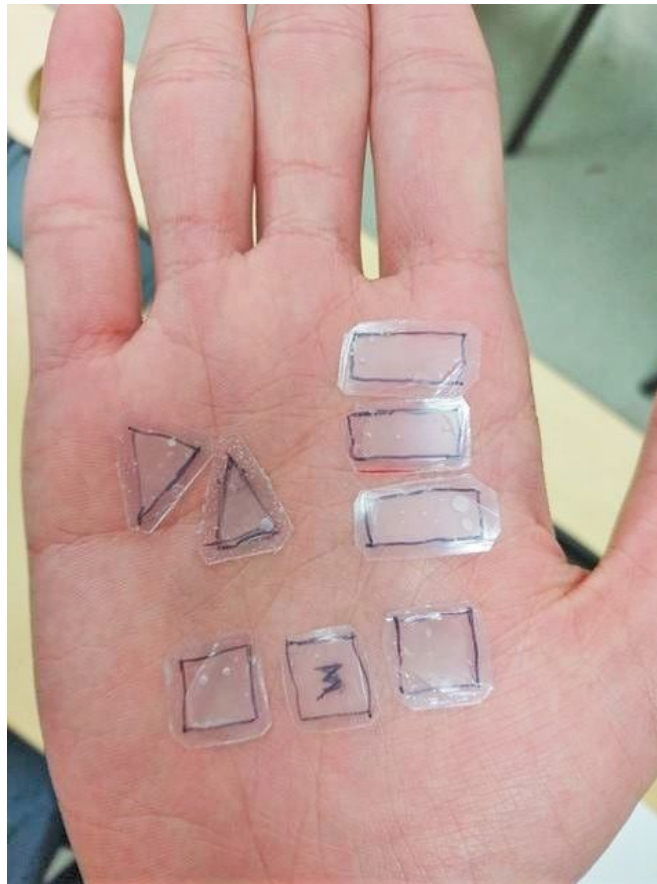
***Note 2:** This is a pretty reliable method. The seal works great most of the time. Poking more than 1 hole in the patch happens once in awhile. The patch stays on well most of the time. The water will leak when you put on if the seal is not good enough, or if there’s another hole you accidentally poked.

WEDNESDAY, AUGUST 31ST

- David made some more mice patches for Thursday

THURSDAY, SEPTEMBER 1ST

- David put 3 patches of different shapes (square, rectangle, and triangle) on the mice in Dr. Jenne’s lab and reinforced them with tissue glue.

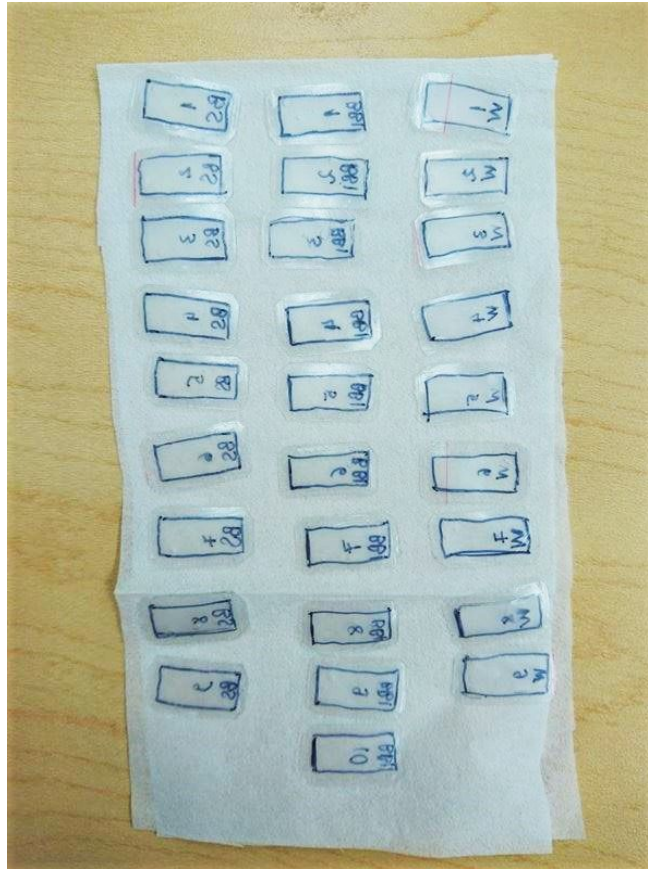


FRIDAY, SEPTEMBER 2ND

- All 3 patches from yesterday survived. The rectangle and triangle worked better than the square. Rachelle from Dr. Jenne's lab said the rectangle looked best.

TUESDAY, SEPTEMBER 5TH

- David created 28 patches for the mouse testing with 9 containing water, 9 containing bacteria and 10 containing pure BBI



RESEARCH

Papers:

<http://www.ncbi.nlm.nih.gov/pubmed/21139238>

- Hydrophilic large molecular compounds
- Via hollow microneedles
 - Loaded into lower epidermis and superficial dermis
- Release rates (Fick's Law of Diffusion)
 - Increase volume of FD-4 injected - faster the FD-4 release rate from skin
 - Release rate increases when FD-4 given in multiple injections
 - Large molecule = lower release rate from skin
- Silicon - useful material?
- Questions:
 - So is the drug being released secreted out of the skin after secretion?

<http://www.ncbi.nlm.nih.gov/pubmed/22575858>

- Sections 2.4, 3.1, 2
- Pressure gradient - greater pressure causes drug to flow through
- Diffusion gradient
- Questions:

- Based on methods of delivery - silicon; have to test and make sure peptide/fluid/bacteria doesn't react with silicon
 - Simulate a large scale prototype of design to test if we can use pressure/diffusion to get the peptide to flow through
- Problem:
 - For microneedles that use multiple needles (our suggested form):
 - 1 microneedle leaks
 - Pressure can't be equally applied to all needles
 - Fluid won't flow through all microneedles equally
 - The small size of microneedles - drugs given on/within microneedles limited to microgram dose
- Applications of microneedles
 - Biotherapeutics, drugs (peptides, proteins, DNA, RNA)
- Hollow microneedles - used for insulin delivery in both rats and humans
- Diffusion and active infusion worked, decreased blood-glucose levels after injection
- Humans found it to be:
 - Decreased pain
 - More preferred (compared to normal needles)
 - Increased insulin pharmacokinetics almost 2-fold - may cause better control over post plasma glucose levels
 - Had faster insulin absorption and enabled more rapid onset and offset metabolic effect on blood glucose levels than injection

https://www.researchgate.net/publication/228562173_Side-Opening_Hollow_Microneedles_for_Transdermal_Drug_Delivery

- Proposed design - measurements for diameter length of needle, etc.
- pump/syringe for injection
 - Need to test diffusion; if diffusion doesn't work, use hand to press
- Overdose problem
 - Reservoir patches give tighter control of delivery rates but can have an initial burst of drug release. If the membrane is damaged, there is also a risk of sudden release of drug into the skin and overdose as potentially a larger area of skin is exposed for drug absorption.
 - In a matrix patch, the active ingredient is distributed evenly throughout the patch. One-half of a patch will have half the original surface area and deliver half the original dose per hour. The matrix patch carries less risk of accidental overdose and offers less potential for abuse than the reservoir system.

<http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=659727>

- The principle of operation is based on the pressure barrier that develops when cross section of capillaries change abruptly in neck and expansion regions. This type of gating device in its normal state can only stop flow, but it can be electrically triggered to re-establish flow when used in combination with two electrodes.
- Mechanics: The capillary stop consists of a region of the tube that is necked down followed by a sharp enlargement. When the liquid is first introduced in the reservoir, it wicks in the necked region and abruptly stops at the neck of the outer edge preventing any outer flow. The pressure barrier provided by the stop can be overcome by external pressure to re-establish a flow.

MATERIAL RESEARCH

TUESDAY, MAY 31ST

http://images.alfresco.advanstar.com/alfresco_images/pharma/2014/08/22/ba2e9668-a586-4daf-9179-70f220be6e56/article-18600.pdf

PSA = Pressure Sensitive Adhesives

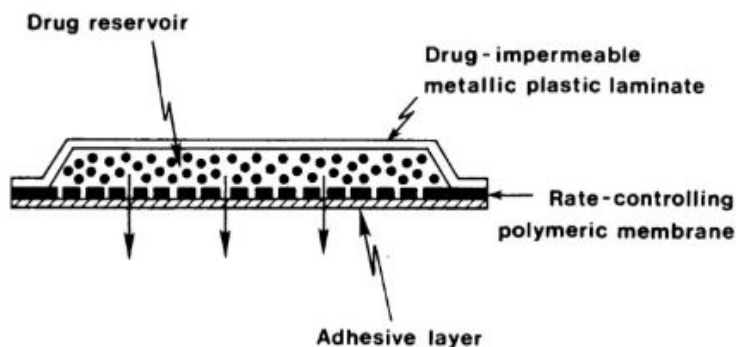
- Materials that adhere to skin with application of light pressure and do not leave residue upon removal
- See paper for materials used
 - Acrylic-, polyisobutylene- & silicone based adhesives commonly used in transdermal patches
- Increasing the polymer content provides a softer and tackier adhesive, whereas higher resin levels result in lower tack but higher adhesion and resistance to cold flow.
- Release liner is peeled off = also has the adhesive properties

Idea to prevent water from leaking out:

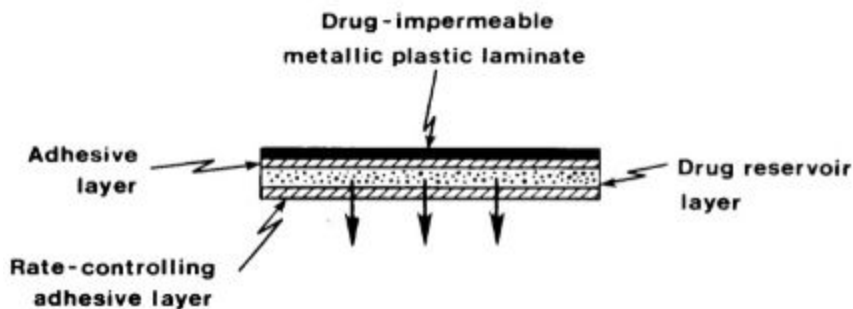
- Adding some sort of liquid in pores that will let peptide through and not let media mix with it
- Gel-like fluid for media

Design of patches:

- Polymer membrane partition-controlled TDD systems
 - There is a constant release as long as concentration is maintained, but release rapidly decline when device approaches exhaustion



-
- Reservoir system
 - Same concept
- Drug in adhesives
 - I don't think this is applicable for us, but would put it here just for reference



- Micro reservoir type
 - Suspension of drug with aqueous solution of water-soluble liquid soluble polymer
 - Homogenous dispersion of drug suspension in a lipophilic polymer (silicone elastomer)

- Example: nitroglycerin patches

Competitors:

- TEPI Patch
 - Articles:
 - <http://futuraerxdream.com.ng/ibuprofen-patch-heralds-side-effect-free-drug-future/>
 - <http://www.painnewsnetwork.org/stories/2015/12/9/new-skin-patch-delivers-pain-relief-with-ibuprofen>
 - 24 hour medication
 - Constant drug delivery for 24 hours
 - The drug is dissolved into the adhesive layer which helped it to release the drug in a steady rate and to take up more drug
 - Will be used for pain medication, so this will be applied to the **SPECIFIC** area where pain is felt
 - Will be out in the market for 3 years

WEDNESDAY, JUNE 1ST

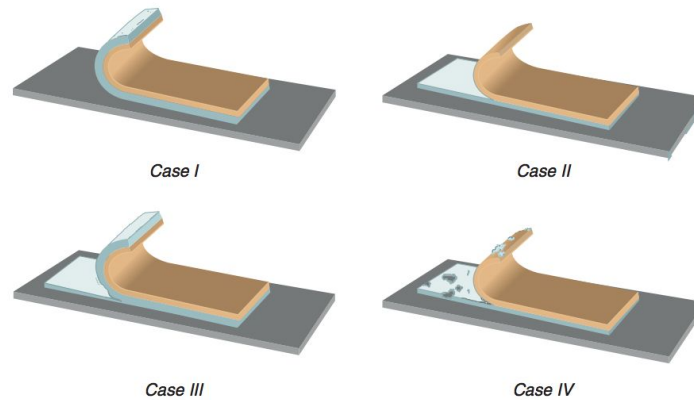
Adhesive layer research:

- <https://geckskin.umass.edu/>
 - Super-adhesive based on mechanics of gecko feet
 - Leaves no residue
 - Not sure if we can get our hands on this though...

FRIDAY, JUNE 3RD

<http://www.tandfonline.com/doi/pdf/10.1517/17425247.2012.637107>

- PSA's fall into three categories: solvent based, water based and hot-melt
 - Solvent based are traditionally used in patch production
- ○ Water based and hot-melt are more beneficial for skin irritation, sensitization and environmental contamination risks
- ○ Polyisobutylenes are better for allergenicity compared to acrylics and silicone-based
- Patch failures:
 - Case I: Adhesive failure
 - Case II: PSA doesn't adhere to backing layer
 - Case III: matrix has good adhesive strength, poor cohesive strength
 - Case IV: adhesive and cohesive failure



- PIB-based adhesives:
 - Disadvantage: easy oxidation and low air and water vapour permeability
- Acrylic-based adhesives:
 - Colorless and transparent
 - More resistant to oxidation
- Silicon-based adhesives
- When testing in vivo performance:
 - Need to find an artificial material that is able to simulate continuous variations of skin humidity - related to critical surface tension, surface roughness and deformability
 - Skin deformability is most critical to consider
 - Effects of relative adherend humidity on peel adhesion performances can be studied using collagen-coated plates
 - When peeling off a patch, need to consider tensile deformation, bending stiffness and substrate deformation
 - Stress distribution on skin deformation was measured in vivo by tension, torsion, suction and indentation tests

Some Market Research:

Paper: **Challenges and opportunities in dermal/transdermal delivery**

From <<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2995530/>>

PATCHES that is applicable in our subgroup:

- Clonidine patches
 - Catapres TTS® was introduced in **1984** for high blood pressure as the first 7-day patch system
 - "The patch should stay in place during showering, bathing, or swimming for a **full 7 days.**" From <<http://www.mayoclinic.org/drugs-supplements/clonidine-transdermal-route/oper-use/drg-20073656>>
 - Clonidine is in a class of medications called centrally acting alpha-agonist hypotensive agents. It works by decreasing your heart rate and relaxing the blood vessels so that blood can flow more easily through the body. From <<https://www.nlm.nih.gov/medlineplus/druginfo/meds/a608049.html#precautions>>

- o How did they solve the problem with loss of adhesion? "If the clonidine patch loosens while wearing it, apply the adhesive cover that comes with the patch. The adhesive cover will help to keep the clonidine patch on until it is time for the patch to be replaced. If the clonidine patch significantly loosens or falls off, replace it with a new one in a different area. Replace the new patch on your next scheduled patch change day."

From

<<https://www.nlm.nih.gov/medlineplus/druginfo/meds/a608049.html#precautions>>

- Climara patches
 - o Treating conditions due to menopause (eg, hot flashes; vaginal itching, burning, or dryness), treating vulvar and vaginal atrophy, and preventing osteoporosis. It is also used for estrogen replacement therapy after failure of the ovaries and to relieve symptoms of breast cancer. From <<http://www.drugs.com/cdi/climara-weekly-patch.html>>
 - o Method of application: A new patch should be applied to your skin on the same day once a week (i.e., the patch should be changed once every 7 days) From <<http://chealth.canoe.com/Drug/GetDrug/Climara>>

TUESDAY, JUNE 7TH

isosorbide dinitrate (ISDN) Patch

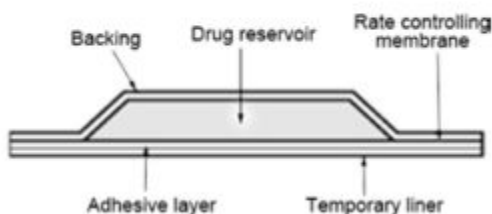
<http://www.scielo.br/pdf/bjps/v51n2/1984-8250-bjps-51-02-00373.pdf>

***They are dealing with a drug called isosorbide dinitrate (ISDN) which is used as vasodilator for angina, congestive heart failure, and esophageal spasms.

What they are trying to create:

- **Acrylate polymers** = they used this as the rate controlling membrane, as this polymer has not been extensively used in patches before
 - o **Why use this?** keep drug release for at least 48 hours at constant rate

Here's how their patch looks like: poor mouse :(



- Patch was stored in a sealed aluminium pouch = minimise the loss of solvent

Part of the Patch	Brand or what material was used	Why was it chosen	
Backing layer		Same material as what is existing	Temporary liner and the backing layer were then

			heat-sealed and cut to the appropriate sizes
Temporary Liner	3M, Scotchpak 1022	Packaging purposes, protects adhesive	Adhesive solution was coated onto the temporary liner (3M, Scotchpak 1022), allowed to dry completely
Rate controlling membrane	Polyacrylate membrane (made from scratch), synthesised by 2-hydroxy-3-phenoxypropylacrylate, 4-hydroxybutyl acrylate and diethyl maleate	To keep drug release for at least 48 hours at constant rate Better permeation, does not involve degradation, erosion or dissolution of the polymer	These are non-degradable polymers Thickness: 14 microns Pore sizes are fabricated randomly by polymer chains
Reservoir layer	75% PVA, 10% ISDN and 5% urea	Showed better permeation Permeation rate is increased by 25.4 fold, a 31.1-fold cumulative release after 24 h, and a 30.8-fold cumulative ratio of release at 24 h compared to EC	Also has the penetration enhancers
Adhesive layer	PSA (pressure sensitive adhesives): 5% ISDN dispersed in the mixture of PVP K90, PEG400 and gelatine	This whole combination helps enhance drug permeation	
THEIR CONCLUSION	This presented a longer release time at a sustained release rate Would promote patient satisfaction Sustained release rate, owing to the rate-controlling membrane, A higher loading-drug amount, owing to the separated drug reservoir layer Easier to tune release rate and release time to achieve the prediction		

Patch 2:

Contraceptive patch <http://www.google.com/patents/WO2013112806A2?cl=en>

Dosage: 20 mg per day, \$14 for a full month of medication



Pros about this patch		Cons about this patch
Entire patch is flexible enough to effectively and comfortably adhere to contoured sites of the body Used destrogel mixed with carriers		
Part of the patch	Material used	Why did they use it
Backing layer		
Release liner		
Adhesives	Duro Tak® 87-4098 by Henkel Corporation., Bridgewater, N.J. Comprises a certain percentage of vinyl acetate co-monomer PIB adhesives such as 0.1 to 30 wt% PVP (i.e., povidone) or a PVP co-polymer such as PVP/VA (i.e., copovidone) as a humectant and plasticizer	PVPs are very hydrophilic as compared to PIBs, which are hydrophobic, has an ability to absorb moisture. The use of PVP copolymers, such as PVP/VA, can improve compatibility with other polymers and modulate the water absorption.

Recommendations:	WHY
use of water soluble polymers is generally less preferred	Would cause dissolution or erosion of the matrix Would affect the release rate of the desogestrel Would affect capability of the dosage unit to remain in place on the skin
Incorporate cross-linking monomeric units or sites	Would solve problems with polymers having glass transition temperatures below room temperature which are used to form a polymer matrix as the transdermal desogestrel-containing composition

In development of suitable polyisobutylene PSAs, one consideration is that PIBs are not crosslinked so they flow slightly.	Within a patch, that slight flow can cause an unsightly ring around the patch when it is worn for several days.
A higher content of high molecular weight PIB in the PSA formulation. **Polybutene in certain PIB formulations, such as the Oppanol B-12 functions as a plasticizer to allow for incorporation of more high molecular weight PIB. Mineral oil can be used as a plasticizer for the same purpose.	

WEDNESDAY, JUNE 8TH

<http://www.technicaljournalonline.com/ijpsr/VOL%20II/IJPSR%20VOL%20II%20ISSUE%20I%20JANUARY%20MARCH%202011/IJPSR%20VOL%20II%20ISSUE%20I%20Article%2019.pdf>

Polymer requirements:

- Biocompatible + Chemically compatible -> with both drug and body

Different companies use different polymer systems:

- Alza Corporation: EVA (Ethylene Vinyl Acetate) or microporous polypropylene
- Searle Pharmacia: Silicone rubber

Backing Layer: Most common is Polyester-polyethylene composite

Rate controlling membrane:

- EVA: The percentage of VA can be manipulated. Higher VA -> higher permeability and higher polarity. Maximum VA is 60% by weight (or else glass transition temperature will increase)
- Silicone rubber: Biocompatible, ease of fabrication, high permeability (especially steroids), free rotation around silicone rubber backbone -> Low microscopic viscosity within polymer

Adhesive: (also referred to as PSA) We talked about PIB today

Release liners: Fluoropolymers

MONDAY, JUNE 13TH

Media Release Material

Water Soluble Materials

- Aquasol uses a mixture of sodium carboxy cellulose and wooden pulp to create the water soluble material
- Aquasol specifically designs their packaging to biodegrade over time or with the introduction of water at any various temperature
- Monosol is another company which specializes in the use of water soluble packaging and dispersible materials. The water soluble film is made from PVOH (Poly Vinyl Alcohol)
- Like Aquasol, the material is water soluble at all temperatures. At higher temperatures, the material is more soluble. That is why they suggest moderate temperatures of 10-20 degrees celsius with relative humidity of 30-60%

- With the material being quickly degraded, water soluble materials are not the best materials to use for the media release. The material however does not harm the environment as the bacteria naturally found in wastewater can break it down into harmless components
- As well, there are no specifics about their material as you have to customize it to your needs

Polyethylene and Bubble Wrap

- An alternative would be to use a single layer of polyethylene used for bubble wrap. By filling the media bubble with media and air, it'll form a pouch that can be popped.
- Polycell makes a bubble wrap called Oxo-B Eco Bubble which incorporates their Reverte Oxo Biodegradable into their polyethylene resins. After discard, through the use of substantial UV light, oxygen and/or heat it will break down in smaller pieces. These smaller pieces are then broken down further by the ingestion of bacteria and through respiration will degrade the plastic into carbon dioxide and water.
- Will look into plastics that degrade over time

Membrane:

- Contacted Dr. Mintchev for a meeting about transdermal patch + materials.
- Reading this paper: page 13

[https://www.ualberta.ca/~csps/JPPS8\(1\)/N.Udupa/glibenclamide.htm](https://www.ualberta.ca/~csps/JPPS8(1)/N.Udupa/glibenclamide.htm)

- This paper tested EVA 2%, 9% and 19% both *in vitro* and *in vivo*. The trend held true that the higher the % of EVA, the more drug diffuses.
- They also tested ethyl cellulose, Eudragit RS-100 and Eudragit RL-100 but only *in vitro*.
- The drug was glibenclamide to treat diabetes.

Reading this atm:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/12/WC500179071.pdf

Release Liner:

- Needs to be chemically inert with drug penetration, penetration enhancer and water
- 3M Scotchpak 1022
- 3M Scotchpak 9741
- 3M Scotchpak 9742
- 3M Scotchpak 9744
- 3M Scotchpak 9755
 - Fluoropolymer Coated Polyester Film
 - Good for release with silicon skin contact adhesives, acrylate, PIB and rubber based PSA
 - Excellent chemical stability

Adhesives:

Links:

1. [https://label.averydennison.co.za/content/dam/averydennison/lpm/na/en/doc/home/resource%20center/Adhesive%20Overview\(1\).pdf](https://label.averydennison.co.za/content/dam/averydennison/lpm/na/en/doc/home/resource%20center/Adhesive%20Overview(1).pdf)
2. https://www.researchgate.net/publication/51881833_Adhesive_properties_a_critical_issue_in_transdermal_patch_development_Expert_Opin_Drug_Deliv_933-45

The typical adhesive properties include:

- **Initial Tack** - The immediate holding power of the label upon contact with the substrate. A label with high initial tack will grab the substrate quickly. A label with low initial tack will exhibit a low level of adhesion when first applied and may remove cleanly.
- **Ultimate Adhesion** - The ultimate or maximum holding power that the label will achieve as the adhesive penetrates into the substrate. The time required to obtain ultimate adhesion may depend on the stiffness (shear) of the adhesive, the roughness of the substrate and the temperature of the environment.
- **Shear Resistance** - A measure of the internal cohesive strength of the adhesive. The shear of the adhesive is an indication of how soft an adhesive is. A low-shear adhesive (soft) has more of a tendency to flow (resulting in higher initial tack), and has a higher chance that the adhesive will split apart if put under stress. A high-shear adhesive (firm) is less likely to split under stress because of its good internal cohesive strength, and will be less likely to flow (possibly lower initial tack).

- Solvent-based
 - Traditionally used in patch production
 - Good for extended wear
 - Provide tighter hold
 - Stingy
- Silicone-based
 - High oxygen/gas permeability
 - Low pain upon removal to sensitive skin
 - Can be customized to improve chemical compatibility and stability with cationic drugs
 - Increased diffusivity
 - Tendency to cause drug crystallization
- DOW CORNING® BIO-PSA 7-4101 SILICONE ADHESIVE, DOW CORNING® BIO-PSA 7-4201 SILICONE ADHESIVE and DOW CORNING® BIO-PSA 7-4301 SILICONE ADHESIVE that way you can compare the different levels of tack. They are all amine compatible with heptane as the carrier solvent."

 Dow Corning BIO-PSA Silicone Adhesives	Resin/Polymer Ratio	Silanol Content	Typical Solids Content %	Solvent
Standard BIO-PSA				
7-4401*	65/35	High	60	Heptane
7-4402*	65/35	High	60	Ethyl Acetate
7-4501	60/40	High	60	Heptane
7-4502	60/40	High	60	Ethyl Acetate
7-4601	55/45	High	60	Heptane
7-4602	55/45	High	60	Ethyl Acetate
SRS7-4501	60/40	Medium	70	Heptane
SRS7-4502	60/40	Medium	60	Ethyl Acetate
SRS7-4601	55/45	Medium	70	Heptane
SRS7-4602	55/45	Medium	60	Ethyl Acetate
Hot Melt 7-4560	60/40	High	100	None

MATH RESEARCH

DIFFUSION:

Factors affecting diffusivity:

Search up: Chapter 2: Overview of Controlled Release Mechanisms by Ronald A. Siegel and Michael J. Rathbone

- Depends on **size of molecule** and **medium**, as well as the membrane that we're using
- For a hard spherical molecule diffusing through:
Equation: $D = kT/(6\pi a \eta)$
 - a = molecule's radius
 - T = absolute temperature (K)
 - η = solvent viscosity
 - k = Boltzmann's constant (this accounts for intensity of thermal agitation)
- In terms of the medium: in *free volume theory*, each drug, solvent, and polymer molecule contains an impenetrable core that is surrounded by nanovoids, called free volume
 - Thermal motions cause the size of voids to fluctuate. Occasionally, a void becomes large enough for a diffusing molecule to move into or through it
 - Free volume of a matrix depends on its composition
 - Free volume can also be increased substantially by sorption of small molecules, such as water. (sorption is the physical and chemical process by which one substance becomes attached to another)
 - For a molecule diffusing through a water-swollen hydrogel, diffusivity of drug is affected by the viscosity of the water space and also by obstructions placed in the drug molecule's path by the hydrogel chains

MONDAY, JUNE 6TH

What we need to model:

- Oxygen diffusion through the backing layer (outside to inside and vice versa)
- The amount of peptides that go through the rate membrane
- How much force would we apply to the pouches for them to break
- Mixing of media in patch and in pouches
- Start modelling the system
 - Play around with the sizes of the packets
 - Do math around, having some idea about how something works would be necessary, at least we have an idea how it works
 - Determine what we're actually trying to solve
 - MATLAB = useful way we could deal with our model - trying different values for a parameter we don't know about and see how it changed, identify what it represents, it's a framework of understanding which parameters are important

FRIDAY, JUNE 10TH

Rate of release of therapeutic agents from reservoir transdermal systems:

- <https://www.researchgate.net/file.PostFileLoader.html?id=55f196f8614325b8798b456f&assetKey=AS%3A272146475778050%401441896184273>
- Assuming mechanism of drug delivery involves these steps:
 - Drug dissolution within the reservoir matrix
 - Drug diffusion and partitioning into the membrane
 - Drug diffusion within the membrane and partitioning into the adhesive layer
 - Drug diffusion within the adhesive and partitioning into the stratum corneum
- Rate controlling membrane controls drug diffusion into the adjacent adhesive layer and therefore is the rate-limiting step in the diffusion process

$$\frac{dM}{dt} = \frac{K_{m/r} K_{a/m} D_a D_m}{K_{m/r} D_m h_a + K_{a/m} D_a h_m} C_R$$

Where:

C_R is the drug concentration present in the matrix,

$K_{m/r}$ and $K_{a/m}$ are the reservoir/membrane and membrane/adhesive partition coefficients,

D_m and D_a are the diffusion coefficients of the drug in the rate controlling membrane and the adhesive layer, and

h_m and h_a are the thicknesses of the rate controlling membrane and the adhesive layer.

<https://www.quora.com/Why-arent-patches-used-as-drug-delivery-systems-more-often>
<http://ceaccp.oxfordjournals.org/content/7/5/171.full>

- Reservoir = drug concentration is established, drug moves further into the skin, into the capillaries, and then into the circulation
- There is a time to reach steady state of plasma concentration

Effect of drug characteristics

The properties of a drug that enable good penetration through the stratum corneum can be deduced from the equation for steady-state flux.² When the cumulative mass of a diffusant, m , passing per unit area through a membrane is plotted, after time t , the graph approaches linearity and the slope yields the steady flux dm/dt ,

$$\frac{dm}{dt} = \frac{DC_0K}{h}$$

where D is the diffusion coefficient, C_0 the constant concentration of drug in donor solution, K the partition coefficient of solute between membrane and bathing solution, and h the thickness of the membrane.

Therefore, for a drug to penetrate well, it should have low molecular mass (high D), adequate solubility in oil (high C_0), and a moderately high partition coefficient. All of the drugs currently available in patch formulation share three features that enable administration through a convenient area of skin: molecular mass <500 Da; high lipophilicity; and low required daily dose (<2 mg). The comparison of the physicochemical properties of fentanyl, buprenorphine, and morphine (Table 2) demonstrates why fentanyl and buprenorphine are suitable for transdermal delivery.³

Parameters that we have to consider:

- Diffusing peptide must not affect the adhesive and vice versa
- Skin compatibility, chemical compatibility
- Tack, peel adhesion, skin adhesion and cohesive strength
- Hydration of skin
 - Tissue swells when skin is saturated with water and its permeability increases = this would be an important factor to increase penetration
- Temperature
- Diffusion coefficient
 - Diffusion speed of molecules depend on the state of matter in the medium
- Drug concentration
 - Drug permeation usually follows the Fick's law. The flux of solute is proportional to the concentration gradient across the entire barrier phase
- Partition coefficient
 - Important in establishing flux of drug through stratum corneum
- Molecular size

Permeability Coefficient Is the Critical Predictor of Transdermal Delivery

$$\text{Transport} = \text{Flux} = (\text{mg}/\text{cm}^2/\text{sec}) = P \times A \times (C_d - C_r)$$

$$\text{Permeability Coefficient} = P = \frac{D \times K}{h} \text{ (cm/sec)}$$

Where A = Surface area of patch
 D = Diffusivity of drug in membrane (skin)
 K = Partition coefficient (patch/skin)
 C = Concentration in donor or receptor
 (patch or skin)
 h = Thickness of membrane (skin)